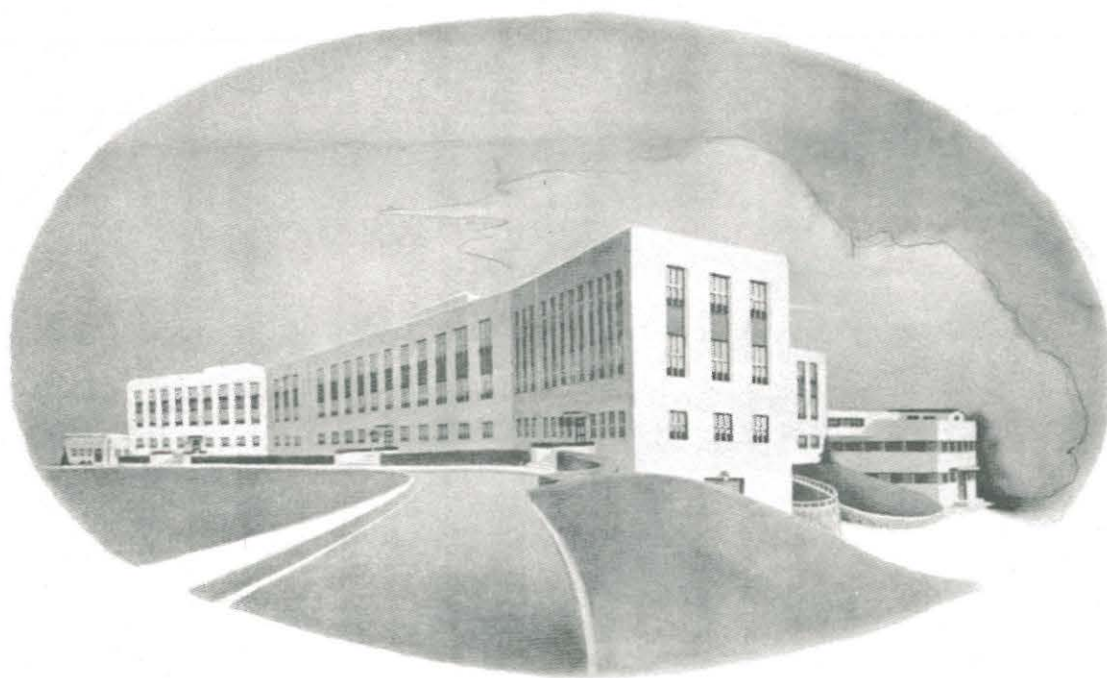


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TIMING BEHAVIOR IN THE ASSESSMENT OF ADAPTATION
TO NITROGEN NARCOSIS

J. Michael Walsh and Arthur J. Bachrach

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Research Report

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Behavioral Sciences Department
Naval Medical Research Institute
National Naval Medical Center
Bethesda, Maryland 20014

ABSTRACT

Research in psychological changes associated with hyperbaric pressure--particularly the behavioral changes identified as "nitrogen narcosis"--has yielded varying and often inconsistent results. One phenomenon reported frequently in nitrogen narcosis is an acclimatization or adaptation to the conditions of the dive; thus, "experienced" divers are found to be less effected by narcosis. Precise quantification and identification of the behaviors and the environmental conditions under which they occur has been lacking in most hyperbaric studies dealing with adaptation to narcosis. The present study is a preliminary one dealing with an experimental analysis of time behavior, using operant conditioning techniques. Timing behavior in albino rats is found to be disrupted in an initial exposure to 200 feet on air. Subsequent exposures reveal gradual adaptation to the chamber conditions, with return to levels of performance close to surface control. Further systematic research is needed to assess behavioral effects of various gases and depths.

Walsh, Bachrach

KEY WORDS

timing behavior

hyperbaric pressure

nitrogen narcosis

operant conditioning

acclimatization

adaptation

hyperbaric animal research

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Behavioral Sciences Department
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More than a century has passed since it was first observed that under certain conditions the air we breathe is capable of inducing narcotic-like effects. Since that time it has been well established that the respiration of air at elevated pressures may be accompanied by behavioral changes characterized by a euphoric "intoxicated-like state" (or "narcosis"), a lack of neuromuscular coordination, amnesia, and a general slowing of cognitive functioning.^{6,21,9} These effects are not limited specifically to air but can be seen with all the "inert" gases if the pressure is raised sufficiently. Over one hundred years have elapsed since the first reported observation yet many aspects of this phenomenon remain obscure and unknown.

From Bureau of Medicine and Surgery, Navy Department, Research Subtask M4306.03-2040D. The opinions and statements contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

This experiment was conducted according to the principles set forth in the "Guide for Laboratory Animal Facilities and Care," prepared by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences, National Research Council.

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EFFECTS OF NARCOSIS

One of the earliest reports of the observation of narcotic symptoms resulting from breathing compressed air came from France in 1834.¹⁶ Over the next 90-year period similar subjective descriptions of behavioral changes are sprinkled through the literature.^{13,10,14,11} It was not until the mid-1930's, however, that any effort was made to measure these changes.

Originally these studies¹¹ began in response to the increasing number of medical problems experienced by tunnel workers and divers. Compressed air was being used by engineers to hold back water when building foundations for bridges and when tunneling under rivers. A major problem appeared to be psychological changes in the workers.

An experiment to assess some of these changes was reported by Behnke, Thomson, and Motley⁶ who presented a description of the "severe psychic" changes involving decrements in mental arithmetic and performance on a pursuit rotor task which occurred at the shallow depth of 100 feet. Subjects reported "a definite euphoria," but with effort normal conduct was maintained. Behnke and Yarbrough⁷ compared the "mental" effects of argon, nitrogen, and helium on a depth estimation task. Argon was found to yield the greatest "mental aberrations," helium the least, and the effect of nitrogen was intermediate. Shilling and Willgrube,²⁴ using U. S. Navy divers breathing compressed air, found that latency to solve mental arithmetic and the number of errors made increased with atmospheric pressure. Based on subjective observations these authors suggest that diving experience lessens the "subjective effects of pressure" (i.e., euphoric sensation), and that intelligence is a factor in performance

decrements (i.e., higher intelligence shows less decrement). To evaluate impairment of performance under relatively low nitrogen pressure Kiessling and Maag¹⁷ used three performance measures (choice reaction time, Purdue Pegboard, and a conceptual reasoning task requiring classification of 32 wooden blocks). Results indicated significant decrements at 100 feet on all measures compared with sea level baselines; furthermore, the amount of decrement appeared to be a function of task complexity, with tests of conceptual reasoning and immediate memory showing greater impairment than tests of simple motor skills or choice reactions. Other investigators have used similar tasks with varying results.

Investigators such as Adolfson^{1,2,3} and Adolfson and Muren⁴ carried out research at depths ranging from 100 to 400 feet. Using tasks such as hand-foot dexterity, mental arithmetic, and reaction time, they found broad behavioral decrement at the greater depths including apparent hallucination. Psychomotor impairment was significant by 300 feet, behavioral disruption by 400 feet. Intersubject variability, they observe, made it impossible to classify symptoms.

All of these studies reported used subjects performing relatively standardized tasks while breathing air in a hyperbaric chamber. Miles and Mackay²² carried out similar tests in the open sea with divers in diving dress performing arithmetic and memory tests at depths ranging from 100 to 180 feet. These researchers found no significant impairment in the general group, although single subjects showed impairment. Bennett,⁸ in commenting on this study, observes that the difference between the open sea and chamber studies "may be due to the nature of

the tests used or that the subjects were well-trained divers (p.8)."
This comment parallels the observation by Shilling and Willgrube²⁴
that experienced divers were less subject to effects of pressure.

Inconsistency is the word which best describes the body of literature concerned with "narcosis." Exhaustive reviews of this literature,^{20, 8,19,15,9} have revealed that although a tremendous amount of research has been completed, relatively few conclusive findings have been presented. In 1956 the National Research Council Panel on Underwater Swimmers made a statement which still holds true today:

Even though the existence of a central narcotic effect has been recognized for many years, much more information is required. The actual types, degrees, and consequences of functional impairment produced by nitrogen at various partial pressures remain ill defined. The extent of individual variation in susceptibility needs to be ascertained (p. 10).

Despite the last 40 years of concentrated investigations many questions have been left unanswered. Adaptation, recovery, predisposition, and even the specific limits of depth at which this phenomenon occurs, are factors which are not clearly defined.

Jennings,¹⁵ in a comprehensive review of nitrogen narcosis, proposed that the effects of nitrogen at pressure are reflected systematically in the overall behavior of the organism. Therefore, single measures (e.g., EEG, pursuit rotor, free association) may not reflect the totality of the effects. The time has come to begin evaluating these behaviors with precise quantification so that the responses and the conditions under which they appear and under which they are maintained and modified, may be better understood.

PROBLEMS IN COMPARING RESEARCH RESULTS

A fundamental problem in all of these studies is the experimental methodology. We have a variety of tests--some standardized (such as the Purdue Pegboard), others apparently created especially for the particular experiment with only face validity and reliability. We do not have any indication of the precise instructions given--and we know that instructions can predetermine results. Measures were frequently crude and subjective observations by the experimenter rather than quantitative assessment. Bennett,⁸ in commenting on the 1962 study reported by Kiessling and Maag,¹⁷ underscores an important point:

The authors pointed out that 'the degree of performance impairment is largely a function of the test used.' This may appear self-evident but many workers ignore this fact and make dogmatic conclusions as to the depth or pressure at which narcosis first appears. Thus, the critical pressure for the onset of narcosis varies with different workers between 100 and 200 feet (p. 7).

Perhaps this discussion so far has been too critical, however, the importance of approaching so crucial a problem as impairment at pressure (at high-risk) with rigorous and meaningful experimental techniques cannot be underestimated. We are left with several conclusions:

1. The failure to establish standardized response measures and experimental procedures has made it nearly impossible to make comparisons across studies.

2. The frequent lack of rigorous experimental control has yielded results which vary from experiment to experiment. Therefore, only very general statements have been made about the phenomena of "narcosis."

3. At present our technological depth capability has far surpassed our psychological and physiological knowledge of the effects of deep diving. Much more information is needed about these phenomena.

CURRENT BEHAVIOR TECHNOLOGY

In recent years a technology of behavior has been developed^{28,12} that allows for quantifiable, controlled, highly predictable patterns of behavior from simple responses to complex chains of responses. These techniques yield an extremely high degree of experimental control which makes possible the systematic study of behavioral phenomena in the individual organism. These operant techniques can be used to detect changes in a wide variety of behaviors, both sensory and motor, and as noted, from simple to very complex. These methods also have been used extensively in the screening and basic assessment of pharmacological agents.^{27,29}

Our reasoning was that these techniques could be applied to another type of manipulation of the psychophysiological state of the organism--hyperbaric pressure. To establish precise behavioral measures to assess effects of hyperbaric pressure in air we decided to design an experiment in which a fine discrimination was required, allowing for a quantifiable assessment of change under clearly defined environmental conditions over time. The experiment to be reported is a preliminary one, as much designed to test out the methods of experimenting under these conditions as for any other purpose. For reasons of experimental control as well as the possibility of comparing the data with related experiments, the ubiquitous white rat was chosen as the experimental subject recognizing

that generalizations to human behavior are to be approached with considerable caution.

METHOD

Two experimentally naive male albino (NMRI-0, Sprague Dawley-derived) rats maintained at 80% free feeding weight (approximately 375 gms) served as subjects. Water was always available in the home cage. Food intake was limited to 14 gms per day to maintain weight; an animal not receiving full food allotment during the experimental session received the remainder immediately after the session in the home cage.

APPARATUS

The basic operant apparatus was a Harvard Instrument Company rat cage (8 1/2 inches wide x 9 1/2 inches long x 8 inches high) made with aluminum front and back panels and perforated plexiglass sides and top. The floor of the box is comprised of 18 (1/16-inch) stainless steel rods, with a stainless steel drop pan 2 1/4 inches below the grid. Two Lehigh Valley mouse levers are mounted on the front panel 1 inch above the grid and 1 inch from either of the side panels. A brass food hopper (Scientific Prototype) is mounted 1/2 inch above the grid and in the center of the panel equidistant from each of the levers. The food hopper is attached by a short rubber tube to a Gerbrands pellet feeder which dispenses 45 mg Noyes pellets as reinforcement. Mounted above each lever and the food hopper are stimulus lights with interchangeable colored plastic covers. The entire apparatus (box, feeder, etc.) is mounted on a sheet metal base with all electrical connections to the apparatus terminating on a blue ribbon connector mounted on the end of the sheet

metal base. Programming is controlled by BRS solid state equipment.

During training and most baseline sessions, the apparatus was mounted on steel slides inside a BRS rat housing which is a sound-reducing airtight enclosure, 18 1/2 inches high x 29 inches wide x 16 inches deep, with a filtered ventilating fan.

All of the pressure runs and some noise control sessions were conducted with the basic apparatus mounted on a set of slides inside a Bethlehem hyperbaric chamber. The chamber is cylindrical with internal dimensions of 42 inches in length and 18 inches in diameter. The chamber can withstand internal pressures of 1,000 pounds per square inch (psi) which is comparable to a depth of 2,245 feet of sea water. The chamber is penetrated with several threaded openings for pressure-fitted connectors to the gas supply and the various programming instrumentation associated with the test apparatus. Across the upper inside surface of the chamber is a metal plate with heating and cooling coils which are thermostatically controlled to maintain constant temperature. The breathing mixture throughout the experiment was compressed air (i.e., nitrogen 78.1%, oxygen 20.9%, argon .9%, carbon dioxide .03%, other rare gases .003%).

PROCEDURE

Both animals were run every day, 7 days a week. Each animal was trained to press a bar for food reinforcement. Rats were reinforced for spaced responding. Under this schedule an animal was reinforced for a single response which followed the preceding response by at least 18 seconds, but not more than 24 seconds. This is referred to as a

Differential Reinforcement of Low rates schedule (DRL) with a limited hold specification.¹² The limited hold allows a specified limited time period when reinforcement is available--in this case, 6 seconds. All responses that occur outside this limited hold period (i.e., 1-17 or 25-00 seconds after the preceding response) go unreinforced and serve to reset the timing period for the next response. This type of schedule generates a very low steady rate of response which is very sensitive to independent manipulations.²⁶ Rats (as well as humans and monkeys) can develop extremely precise timing behavior on DRL schedules.¹⁸

After stable baselines were achieved on each of the schedules the animals were exposed repeatedly to hyperbaric pressure equivalent to 200 feet of sea water. At least one control session at ambient (surface) pressure was conducted between experimental dives to regain baseline performances. "Auditory control" sessions were also conducted where compressed air was bled into the chamber for a duration equivalent to an experimental dive; all valves were open so that ambient pressure was maintained and only noise level was manipulated.

The duration of each experimental dive was approximately one hour and 45 minutes. Compression (descent) rate was constant at 10 ft/min. Time at depth was one hour. Decompression (ascent) rate was 10 psi/min with 3-minute stops at 59,34,14, and 6 psig. Extremely conservative compression and decompression rates were used to maintain temperature (range 24-26° C) and to insure the safety of the subjects.

RESULTS

Figure 1 shows a cumulative record of typical baseline performance on the DRL 18 sec LH6 sec schedule and clearly indicates the animal's precise discrimination. The effects of repeated exposure to a depth of 200 feet are clearly evident in the cumulative records displayed in Figure 2. (See Figure 3 for explanation of cumulative record.) Between each experimental dive baseline control rates (at ambient pressure) were regained, usually within a single session. It is apparent that with each subsequent exposure to hyperbaric pressure behavior began to undergo some kind of adaptation. Varying the intervals between dives did not appear to interrupt the adaptation process, at least with delays up to 12 days. Results of auditory control "dives" showed only momentary changes in behavior at the onset and offset of the auditory (gas hiss) stimulus. Therefore, the observed changes in experimental dives could not be due to changes in noise level.

Figure 4 shows a typical Inter-Response Time (IRT) frequency distribution for the baseline control rate and the five experimental dive sessions. The control session distribution shows the classical DRL bimodal function with the first mode occurring in the initial category (0-2 seconds) followed by a drop in frequency to almost zero, and then a rise to peak at the point where the shortest reinforced IRT occurs (i.e., 18 seconds), followed by a rapid decline. The presence of a well-established temporal discrimination is obvious in the baseline control distribution. In the distribution for Dive 1 the frequency of responding increased approximately three times the baseline rate and the distribution

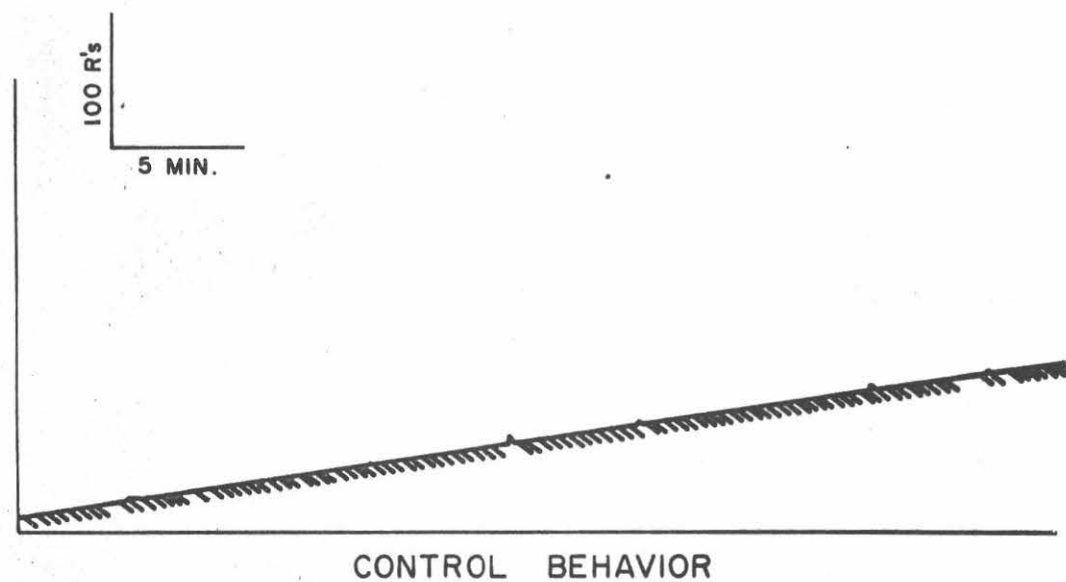


Figure 1. Cumulative performance on DRL Schedule: Surface Control.

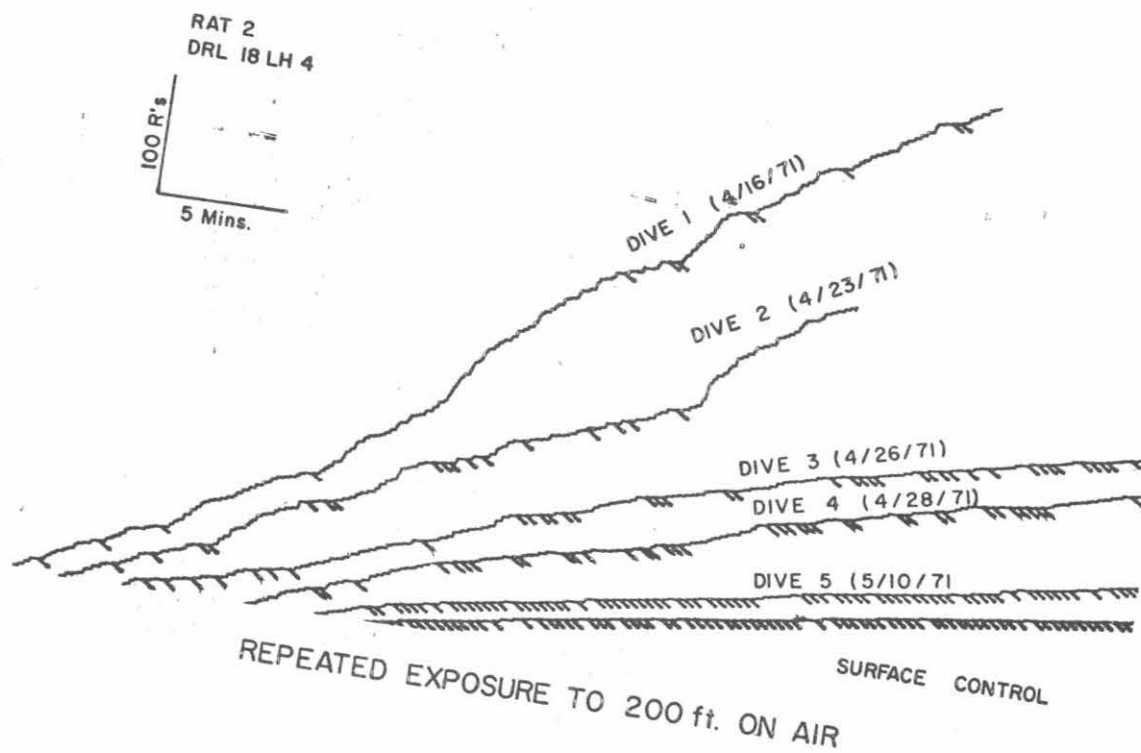


Figure 2. Repeated Exposure to 200 feet on Air.

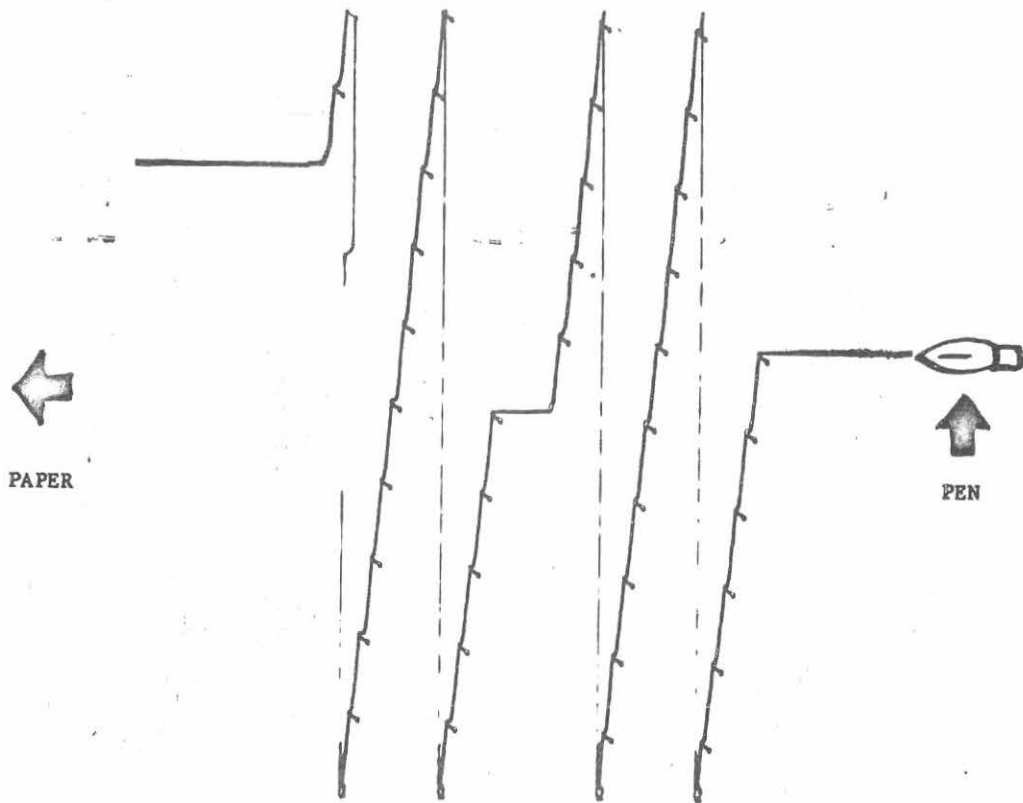


Figure 3. Diagram of a CUMULATIVE RECORD. The paper MOVES from right to left while the pen moves up one step each time the rat responds on the lever. The paper moves at the rate of 12 inches/hr. The downward strokes of the pen, called "pips," indicate reinforcement. The higher the rate of responding, the steeper the slope recorded by the pen. The pen resets after each excursion to the top of the paper (i.e., 500 responses).

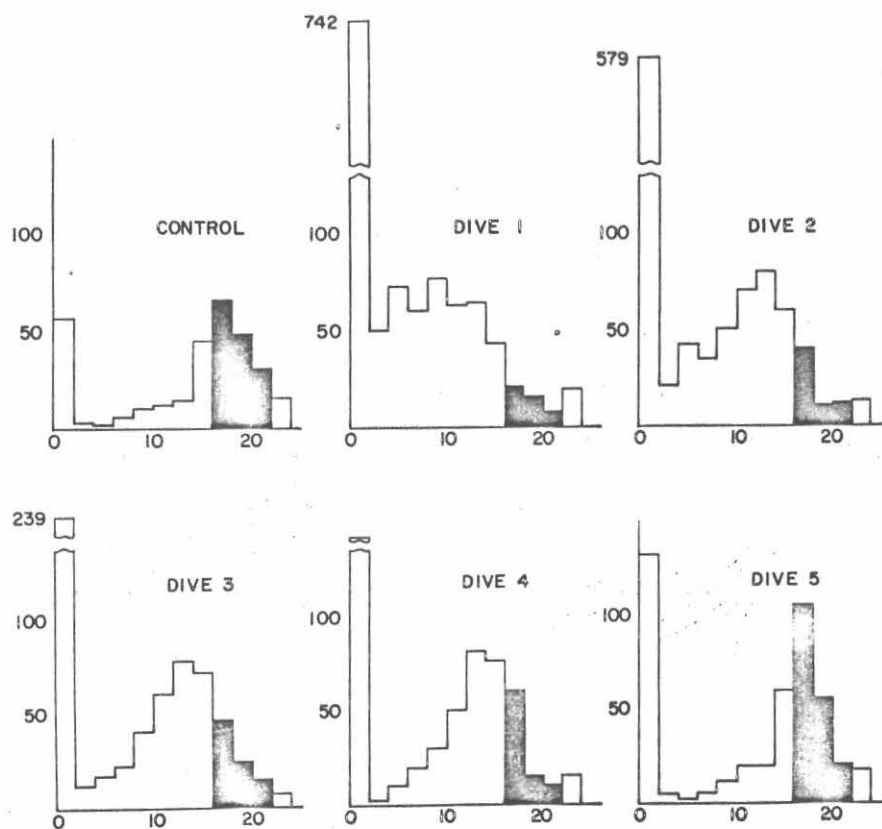


Figure 4. Frequency Distribution of Interresponse Times.

of responses shifted dramatically to very short intervals. This increase in responding indicates that the motor coordination required to produce the response (bar-pressing) was not impaired. The distributions for subsequent dives (2, 3, 4, and 5) reveal that with each exposure to hyperbaric pressure less disruption of the temporal discrimination occurs. With the exception of the shortest interval, the frequency distribution of IRTs for Dive 5 shows the animal to be discriminating at 200 feet with a degree of accuracy comparable to surface baseline performance.

Table 1 contains a detailed breakdown of response frequency (responses/min) over the first 30 minutes at 200 feet for each of the five experimental dives and comparable figures for baseline performance. Response rate was consistent over the 30-minute period except in the initial dive where some bursts of very high rates were emitted. Repeated exposure resulted in smaller increases in response rate up to the fifth dive, where rate stabilized at baseline level.

Table 2 contains a breakdown of reinforcements per minute during the first 30-minute period at 200 feet. Comparisons of Tables 1 and 2 reveal that as rate decreased the number of reinforcements increased.

DISCUSSION

The above experiment demonstrated several facts. Responding and the necessary motor coordination to respond by bar-pressing were not impaired by pressure. Initial exposure to 200-foot depths on air resulted in a marked disruption of temporal discrimination as indicated by the disturbance in DRL spaced responding. Repeated exposures result in what appears to be a gradual adaptation to a point where the animal can perform a complex discrimination without apparent difficulties.

TABLE I.
RESPONSES PER MINUTE AT 200-FOOT DEPTH

		<u>Responses/Min</u>					
		5	10	15	20	25	30
		A	B	C	D	E	F
D	1	10.0	11.2	11.2	21.2	10.4	16.2
I	2	8.4	10.0	8.6	7.6	7.2	17.2
V	3	5.0	5.4	7.0	5.2	4.2	4.2
E	4	7.0	5.0	3.6	5.2	3.8	3.8
S	5	4.4	3.0	3.0	3.4	2.6	2.8
Control		2.9	3.0	2.9	3.1	2.9	3.1

TABLE II.
REINFORCEMENTS PER MINUTE AT 200-FOOT DEPTH

		<u>Reinforcements/Min</u>					
		A	B	C	D	E	R
D	1	.4	.2	.2	.0	.4	.6
I	2	.4	.6	.6	1.0	.8	.0
V	3	.8	.6	.2	1.2	1.0	1.0
E	4	.6	.8	1.0	1.2	1.6	1.2
S	5	1.4	2.8	2.4	1.8	2.4	2.4
Control		2.2	2.1	2.4	2.3	2.4	2.3

Why the first dive engendered so marked a disruption in performance is a matter of conjecture. Ear problems immediately come to mind--the animals were observed frequently to be scratching inside their ears between responding, and perhaps this disrupted discrimination behavior. A more probable explanation, however, is that the initial exposure to hyperbaric pressure had an excitatory effect. In that light a comparison with a known excitatory agent--dl-amphetamine--and its effects may be valuable.

Sidman²⁵ administered dose levels ranging from 1.5 mg/kg to 3 mg/kg of dl-amphetamine sulfate intraperitoneally to rats trained on a DRL schedule requiring spaced responding of 21 seconds. The results are shown in Figure 5 showing Inter-Response Time (IRT).

It may be seen that the saline control illustrates a good discrimination of the required response: a few "burst" responses at the beginning, but the majority of the responses falling around the target time. Increasing doses of the stimulant drug shifted the responses to the shorter periods. Comparing these data to a representative IRT distribution from the current experiment is interesting (see Figure 4).

A similar bursting occurs at the start of the control period but the majority of the responses cluster around the required time. Dive 1 illustrates the marked shift toward shorter response intervals in a fashion quite close to the amphetamine effects. We may conjecture that the initial dive had an excitatory effect that adapted out after repeated exposures.

Schuster and Zimmerman²³ also used rats in a DRL paradigm to evaluate the effects of prolonged treatment with dl-amphetamine. The results of

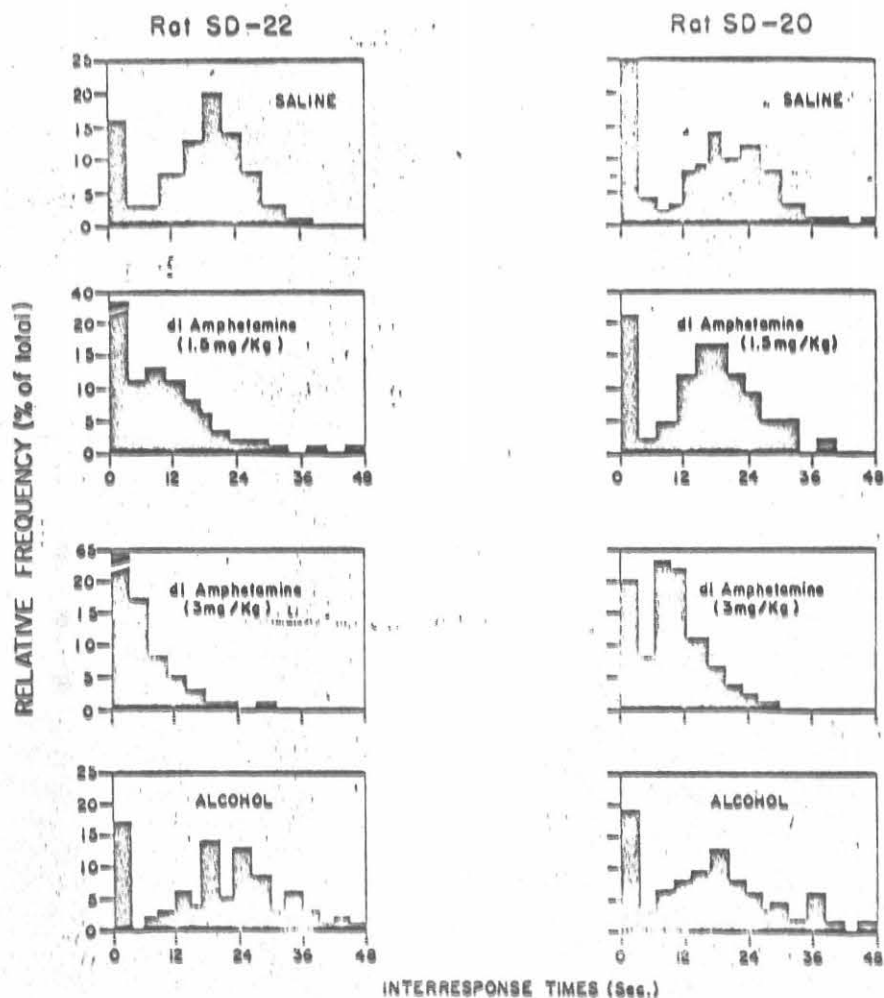


Figure 5. Relative frequency distributions of the time intervals between successive lever presses. Each distribution represents one animal's performance in a single two-hour session. (From SIDMAN (1955))

this experiment showed signs of adaptation or tolerance to the drug; however, other behavioral measures (e.g., activity level) remained at exaggerated levels. This evidence on drug tolerance raises a question about pressure adaptation; is this adaptation process specific to certain behaviors and not to others? The adaptation effect resulting from multiple exposures to hyperbaric pressure does not necessarily indicate physiological tolerance or immunity; only adaptation to a point where a specific chain of behaviors can be emitted.

The effects of pressure may depend in part on the consequences of behaviors and the values of the contingencies controlling the reinforcement schedule. That is, adaptation may only take place in those behaviors where decrements will cause reduction in the probability for reinforcement.

Adaptation, as noted in the discussion earlier in this paper, has been reported by many investigators. Miles²¹ reports that experienced divers do not suffer narcotic episodes, however, weekly dives are necessary to maintain immunity. Bennett⁸ observes that "there is a considerable interindividual susceptibility to the narcosis, whose onset is rapid and to which frequent exposure produces some acclimatization (p. 14)." The mechanism of such adaptation is not understood.

It is very possible that the principle of stimulus (pressure) change may apply in the adaptation process; any novel stimulus may disrupt behavior.⁵ Probable physiological excitation coupled with stimulus change may result in behavioral impairment such as seen in Dive 1 and the amphetamine studies, with the magnitude of the disruption decreasing with repeated exposures. At this point we can only conjecture.

The results of the present experiment have served to lend precision to heretofore described but poorly quantified phenomena. The techniques used herein have provided experimental control needed to attack problems so often subjectively approached in hyperbaric research.

The question still remains, however, whether this behavioral adaptation reflects a broad physiological tolerance to hyperbaric pressure, or simply a behavioral acquisition to this specific environment (i.e., chamber simulation at 200-foot depth). Further research is needed to clarify this issue. Deeper dives on air will determine whether readaptation occurs at greater pressures. The use of a variety of gas mixtures would provide some quantification on the theory of narcosis as a function of the lipid solubility of gases,⁸ and would determine whether initial disruption and subsequent adaptation occur with other gaseous mixtures.

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